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A Multicenter Cohort Study of Histological Findings and Long-Term Outcomes of Kidney Disease in Women Who Have Been Pregnant

Philip Webster[1,4], Louise M Webster[2], H. Terence Cook[1,4], Catherine Horsfield[5], Paul T Seed[2], Raquel Vaz[1], Clara Santos[1], Isabelle Lydon[2], Michele Homsy[2], Liz Lightstone[1,4], Kate Bramham[3]

[1]Imperial College Healthcare NHS Trust, Imperial college Renal & Transplant Centre, Hammersmith Hospital, London, UK

[2]Division of Women's Health, Women's Health Academic Centre, King's College London and King's Health Partners, London, UK

[3]Department of Renal Sciences, Division of Transplantation and Mucosal Biology, King's College London, UK Maternal and Fetal Research Unit, King's College, London, UK

[4]Department of Medicine, Imperial College London

[5]Guy's and St. Thomas' NHS Foundation Trust

Corresponding Author: Dr Kate Bramham

Department of Renal Sciences, King's College London (t) 004420 32996223 (f) 004420 7848 0515 kate.bramham@kcl.ac.uk

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Abstract

Background and objectives For many women pregnancy is the first contact with health services, thus providing an opportunity to identify renal disease. This study compares aetiologies and long term renal outcomes of biopsy proven renal disease identified during pregnancy or within one year postpartum, with non-pregnant women.

Design, setting, participants and measurements Native renal biopsies (1997–2012), in women of childbearing age (16 to <50yrs), from 21 hospitals were studied. The pregnancy-related diagnosis group included those women with abnormal urinalysis / raised creatinine identified during pregnancy or within one year postpartum. Pregnancy-related and control biopsies were matched for age and ethnicity (black vs non-black).

Results 173 pregnancy-related biopsies (19 antenatal, 154 post-pregnancy) were identified and matched with 1000 controls. Focal segmental glomerulosclerosis (FSGS) was more common in pregnancy-related biopsies (32.4%) than controls (9.7%) ($p<0.001$) but there were no differences in Columbia classification. Women with a pregnancy-related diagnosis were younger (32.1yrs *vs* 34.2yrs; $p=0.004$) and more likely to be black (26.0% *vs* 13.3%; $p<0.001$) than controls, although there were no differences in ethnicities in women with FSGS. The pregnancy-related group (excluding antenatal biopsies) were more likely to have a decline in CKD-EPI eGFR in the follow-up period than controls (odds ratio 1.67, 95% CI 1.03-2.71, $p=0.04$), and this decline appeared to be more rapid (-1.33 *vs* -0.56 ml/min per $1.73m^2$ per year respectively; $p=0.045$). However, there were no differences between groups in those who required RRT or who died.

Conclusions Pregnancy is an opportunity to detect kidney disease. FSGS is more common in women who have been pregnant than in controls, and disease identified in pregnancy or within one year postpartum is more likely to show a subsequent decline in renal function. Further work is required to determine whether pregnancy initiates, exacerbates or reveals renal disease.

Introduction

Chronic kidney disease (CKD) is estimated to affect up to 6% of women of child bearing age in high income countries (1). Frequently, antenatal visits are the first time women are assessed by health care, thus providing an opportunity to identify CKD. However, few studies have investigated the aetiology of renal disease identified during or after pregnancy, and to our knowledge none have compared with the spectrum of disease in non-pregnant women. Improved understanding of renal pathologies identified during pregnancy will inform decision making about the necessity of biopsy during or after pregnancy.

Pregnancy is a 'stress test' for the kidney and may lead to progression of pre-existing disease. It is possible that less severe disease may be revealed during pregnancy but there is limited study of natural history of renal disease identified during or after pregnancy to guide long term prognosis and management of young women with newly diagnosed CKD.

Our aims were to define the aetiologies and long-term outcomes of renal disease identified during pregnancy or within one-year postpartum, and compare these with non-pregnant women of child-bearing age.

Materials and Methods

All renal biopsy reports for women of child-bearing age (16 to <50yrs) from five renal units serving 21 referring hospitals (1997-2012) were reviewed. The clinical details of the reason for biopsy were assessed, and pathology records interrogated. Women who were biopsied for abnormal urinalysis / raised serum creatinine (SCr) identified during pregnancy (regardless of the timing of the subsequent biopsy), and all women biopsied within one year postpartum were included in the pregnancy-related diagnosis group. Repeat and inadequate biopsies were excluded. Protein: Creatinine Ratio (PCR) was recorded where available, and quantification in g/24hr was converted to an estimated PCR by multiplying by 100. Albumin: Creatinine Ratio (ACR) quantification were excluded from analyses as they could not be reliably converted to an estimated PCR.

Rate of change of estimated GFR (eGFR) per year was calculated using the CKD-EPI formula (2). Women of mixed race that included black heritage were categorised as black. Women who were on RRT during follow-up were considered to have eGFR of 10ml/min per 1.73m^2 for the purpose of calculating change in renal function over time. In view of the expected physiological fall in serum creatinine (SCr) during pregnancy, for the purpose of assessing eGFR and rate of change in eGFR, comparison was made between controls and post-pregnancy patients only i.e. women biopsied during pregnancy were not included in this analysis due to inaccuracies of GFR estimates in pregnancy (3, 4).

Each biopsy was assigned a primary diagnosis, and additional concurrent diagnoses recorded. If focal segmental glomerulosclerosis (FSGS) was present but deemed to be secondary to an alternative intrinsic renal pathology, cases were categorised according to the primary diagnosis and not FSGS. All pregnancy-related biopsies and all indeterminate cases (including in the control group) were re-reviewed by two histopathologists independently with consensus agreement for diagnosis. All FSGS biopsies (pregnancy-related and controls) were formally classified according to Columbia classification (5). For the remaining controls, the biopsy diagnosis in the original report was used.

Statistical Analyses

Control women were matched against pregnant women by age (at last birthday) and ethnic group (black vs non-black) and unmatched controls dropped. In order to maintain power, all controls matched for age and ethnicity were included. Proportions were compared using two-sided Chi-Square test with Yate's correction, and the non-parametric Mann-Whitney U test was used for non-normally distributed continuous variables. Logistic regression analysis with a dummy variable for matching group was used to adjust for any effect of age, ethnicity, or their interaction on diagnosis and renal outcomes. Spearman's rank correlation was used to explore the relationship between non-normally distributed continuous variables. Statistical analyses were performed using Stata version 14.1 (StataCorp, College Station, Texas) and GraphPad Prism (version 7.0).

Results

1399 biopsies were identified in women aged between 16-50 years, including 173 pregnancy-related biopsies (19 antenatal, 154 post-pregnancy) and 1226 control biopsies, between 1997 and 2012. One thousand control women were matched for age and ethnicity, and included all women with equal ages and ethnicities as the pregnancy-related group i.e. women were not excluded if there was more than one match per pregnancy-related case. Figure 1 shows how the matched cohorts were assembled, and the baseline demographics are shown in Table 1. The median age of women with a pregnancy-related diagnosis was significantly lower than controls, and there was a higher proportion of women of 'black or black British' ethnicity in the pregnancy-related group compared to controls. SCr at the time of biopsy was significantly lower in the pregnancy-related group. There was no difference in urinary PCR between women with biopsies performed post-pregnancy and controls, but PCR in women with biopsies performed antenatally was significantly higher than those performed after delivery (p=0.02), and compared to controls (p=0.02).

Histological diagnoses

Focal segmental glomerulosclerosis (FSGS) was the primary diagnosis in 32.4% (56/173) of pregnancy-related biopsies compared to 9.7% (97/1000) of controls (p<0.001). Lupus nephritis (LN) was found more commonly in controls (23.5% (235/1000) vs 13.9% (24/173), p=0.001) (Table 2).

Women with pregnancy-related FSGS were younger than controls but there were no significant differences in ethnicity or Colombia classification between groups. Creatinine at time of biopsy was significantly lower in the pregnancy-related group. (Table 3). There were no disagreements between histopathologists in diagnoses or Columbia Classifications.

Renal outcomes

The date of delivery was available in 67.5% of biopsies performed after delivery. The median time from delivery to biopsy was 199 days (IQR 92, 312), including nine biopsies performed within six weeks. Follow-up data on renal function were available for 58.4% (101/173) of the pregnancy-related group and 45.9% (459/1000) of the control group (Table 3). There was no difference in the median follow-up time between pregnancy-related and control groups. Women with a pregnancy-related diagnosis (excluding those diagnosed antenatally), were more likely to have an overall decline in eGFR in the follow-up period than matched controls despite adjustment for remaining differences in age and ethnicity between groups (odds ratio 1.67, 95% CI 1.03-2.71, p=0.04). This decline also appeared to be more rapid in the pregnancy-related group (-1.33 *vs* -0.56ml/min per 1.73m^2 per year respectively; p=0.045). There was no correlation between age and rate of decline in eGFR (Spearman's Rho=0.03, n=546, p=0.53). There were no significant differences between the proportion of women requiring RRT between pregnancy-related cases and controls or deaths during the follow-up period (Table 4).

There were no significant differences in rate of change in eGFR in women with FSGS between groups, or requirement for RRT or death (Table 5).

Comparison between antenatal and postpartum biopsies

Median SCr was similar, and urinary PCR higher, at the time of biopsy in women biopsied antenatally compared to those biopsied post-pregnancy (table 1). There were no differences in biopsy diagnoses between groups (table 2) and no difference in those that died or required RRT (table 3).

Discussion

Main findings

This study demonstrates the wide range of glomerular diseases identified by renal biopsy during or within one year of pregnancy, supporting the role of renal biopsy for confirmation of diagnosis in this patient group. FSGS was more frequently reported in pregnancy-related

biopsies than in controls, but no differences in Colombia classification were observed. Conversely lupus nephritis was less commonly identified during or after pregnancy than in controls. Women with a pregnancy-related diagnosis had lower SCr concentrations at time of biopsy than controls, thus pregnancy may provide an opportunity to identify CKD at earlier stages. Women with biopsies after pregnancy also had a more rapid decline of eGFR during follow-up than controls, despite comparable severity of proteinuria, highlighting the importance of detection and diagnosis of renal disease revealed by pregnancy. Nearly one in forty women (2.3%) with a pregnancy-related renal biopsy died and one in eight (12.7%) required RRT during the follow-up period. This emphasises the severity of a diagnosis of glomerular disease in young women, and the substantial implications it has for the individual and her new family.

Strengths and weaknesses

To our knowledge, this is the largest study of pregnancy and post-pregnancy biopsies with secondary histological classification, and the only study to include controls with matching for age and ethnicity. Data were from 21 referring centres hence unlikely to be confounded by centre specific subjective decision making about indications for biopsy. However, the study is unable to address the long-term renal outcomes of other renal diseases identified within one year of pregnancy that do not require biopsy for diagnosis e.g. reflux nephropathy or cystic kidney disease, thus these data relate only to glomerular disease. One of the limitations of our study was the absence of detailed pregnancy data (including parity and diagnosis of pre-eclampsia) hence it was not possible to establish the relationship between pregnancy outcomes and renal biopsy lesions. Furthermore, due to the large number of centres included it was not possible to confirm that all control women had not had a recent pregnancy which was not reported on the biopsy request form. We acknowledge also that follow-up data on renal function was available for approximately half of the pregnant and control groups.

FSGS

FSGS was found in nearly a third of pregnancy-related biopsies, with no differences in Columbia classification of FSGS between pregnancy-related and control groups. FSGS was also the most common diagnosis in postpartum biopsies by Day *et al*, identified in a comparable proportion of pregnancies (28%) but Columbia classification of FSGS was not reported (6). FSGS lesions (7, 8) and 'FSGS-like' lesions (9) have been described in some biopsy series of women with pre-eclampsia, with correlation between severity of lesions and clinical findings (10) .

Unlike animal micropuncture studies (11) which report unchanged intraglomerular pressure during pregnancy, a recent systematic review, using synthesised estimations from formal assessment of renal plasma flow and glomerular filtration rate (GFR), described an increase in filtration fraction in healthy pregnancy (12), thus further exacerbation of haemodynamic changes could contribute to the development of FSGS in pre-eclampsia. However, the proportion of biopsies with the perihilar variant of FSGS, which is the typical pattern of adaptive FSGS in non-pregnant patients (13), was not greater in pregnancy-related cases than control groups in our study, although true discrepancies may not have been identified by the small numbers within classification subgroups.

More recently podocyte loss has been proposed to lead to progressive renal injury in women with pre-eclampsia. Podocyturia is reported in women with pre-eclampsia, prior to, at time of diagnosis and postpartum (14 –16) and downregulation of podocyte-specific proteins (e.g. nephrin, synaptopodin and GLEPP-1) is reported in the renal biopsies of women with preeclampsia (17, 18). Similarly, podocyturia is observed in patients with FSGS (19) and with progression of other glomerular diseases (20). However, there is a regression of histological findings of pre-eclampsia, including complete resolution of 'FSGS-like lesions' after delivery in historic large biopsy series (10, 21). Furthermore, detailed renal physiological assessment of 57 women with pre-eclampsia observed that functional manifestations of glomerular endothelial injury were undetectable after four weeks (22), suggesting that immediate pathophysiological changes secondary to pre-eclampsia may not

be contributory to persistent renal abnormalities in the postpartum period, and that pre-existing renal injury may be important. For example, one in five women with severe pre-eclampsia had underlying renal disease in a biopsy series of 86 women (23) and a wide range of renal pathologies were reported in a population study of renal biopsies performed in pregnancies complicated by pre-eclampsia (24). Moreover, Norwegian population studies have identified pre-eclampsia in a previous pregnancy to be associated with increased relative risk of having a future renal biopsy (24), and developing future ESRD (25) but the risk of progression to ESRD in women with renal biopsies remote from pregnancy is not augmented by a history of previous pre-eclampsia (26) .

Other histological diagnoses

Higher rates of LN were observed in the renal biopsies of the control group compared to women in the pregnancy-related group. A recent systematic review reported an estimated rate of 16.1% (95% CI 9.0-23.2%) lupus nephritis flare during pregnancy (27). However, Day *et al* reported LN to be present in 35% and 8% of biopsies performed in pregnancy and postpartum respectively (6). The lower incidence of LN diagnosed within one year of pregnancy in this study may reflect more women with SLE conceiving with quiescent disease or differences in local practice. For example, due to perceived risks of renal biopsy during pregnancy, some physicians may treat women who develop LN empirically without biopsy.

Progression of CKD

In this study, women with a pregnancy-related diagnosis had lower SCr at time of biopsy than controls, even after exclusion of antenatal biopsies and adjustment for age. Pregnancy is associated with a 50% increase in glomerular filtration thus is a ‘stress test’ for the kidney (28) , and may provide an opportunity to detect early disease. Our study also identified a more rapid decline in GFR in women with renal disease identified within one year of pregnancy despite comparable levels of proteinuria, less severe disease at diagnosis, and adjustment for age and ethnicity. The National Institute of Clinical Health Excellence (NICE)

recommend that the absolute risk of renal disease after hypertensive complications in pregnancy is low and no specific advice or follow-up is required (29), and there are no specific recommendations regarding follow-up of renal disease identified during pregnancy. NICE guidelines recommend that 24-hour urine collection remains the gold standard of analysis of proteinuria in pregnancy; however spot urine PCR is an acceptable alternative therefore both methods were included. There is insufficient evidence on the use of ACR in pregnancy (29, 30) and therefore they were not included in the analysis. The CKD-EPI formula may underestimate GFR in pregnant women (2, 31) hence cases with antenatal biopsies were not included in analyses of renal function. Nine of the postpartum group were biopsied within six weeks of delivery, and a persistent pregnancy related elevation in eGFR may have influenced findings, although this effect is likely to be minimal. It is also possible that nephrology led follow-up of only women with more severe disease diagnosed during or after pregnancy may confound analysis of progression of renal disease, although the inclusion of five renal centres in this study reduces the influence of individual centre policy on selection of women who continued to have nephrological follow-up. The rate of ESRD (12.7%) in women with a pregnancy-related diagnosis was not higher than controls, but appears to be lower than a smaller study of 53 women with proteinuria identified in pregnancy performed over two decades ago (21% progressed to ESRD) (32). In contrast, Day *et al* reported much higher rates of women developing ESRD (30%) after women biopsied antenatally which may reflect differences in thresholds for biopsy or length of follow-up. The high rate of progression of renal disease identified during pregnancy suggests that earlier intervention and nephrology follow-up, even for those with less severe disease, is warranted.

Indications and safety of biopsy

Due to the large number of centres included we were unable to obtain detailed clinical information following the biopsy which is a limitation of this study. Thus we are unable to compare risk of biopsy during or after pregnancy with controls. The decision to perform a

renal biopsy during pregnancy is complex for both the clinician and mother. However, our data and others support the role of renal biopsy either during or after pregnancy as histological confirmation is likely to lead to a change in management in the majority of women (33).

Conclusions

The findings of this study support the use of renal biopsy as a diagnostic tool for the investigation of renal disease identified during or within one year of pregnancy. Pregnancy provides an opportunity for detection of disease and thus prevention of CKD progression and of future cardiovascular disease. FSGS is more commonly found in women who have been pregnant than in controls and furthermore, women with a pregnancy-related diagnosis have a more rapid progression of disease. Further work is required to determine whether pregnancy initiates, exacerbates or reveals renal disease.

Disclosures of Conflict of Interest

None

Acknowledgements

PW, LL and KB were responsible for study design, data collection, statistical analysis and manuscript submission. PTS performed statistical analysis. LMW, IL, MH, CS and RV were responsible for data collection. TC and CH reviewed all renal biopsies and Columbia classified biopsies with FSGS. We acknowledge support from Guy's and St Thomas' NIHR Biomedical Research Centre for KB salary and from Imperial College NIHR Biomedical Research Centre. PTS is partly funded by Tommy's (Registered charity no. 1060508) & CLAHRC South London (National Institute for Health Research).

REFERENCES

1. Mills KT, Xu Y, Zhang W, Bundy JD, Chen C-S, Kelly TN, Chen J, He J: A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. *Kidney Int* 88: 950–957, 2015
2. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J: A new equation to estimate glomerular filtration rate. *Ann Intern Med* 150: 604–12, 2009
3. Alper AB, Yi Y, Rahman M, Webber LS, Magee L, von Dadelszen P, Pridjian G, Aina-Mumuney A, Saade G, Morgan J, Nuwayhid B, Belfort M, Puschett J: Performance of estimated glomerular filtration rate prediction equations in preeclamptic patients. *Am J Perinatol* 28: 425–30, 2011
4. Smith MC, Moran P, Ward MK, Davison JM: Assessment of glomerular filtration rate during pregnancy using the MDRD formula. *BJOG* 115: 109–12, 2008
5. D'Agati VD, Fogo AB, Bruijn JA, Jennette JC: Pathologic classification of focal segmental glomerulosclerosis: a working proposal. *Am J Kidney Dis* 43: 368–82, 2004
6. Day C, Hewins P, Hildebrand S, Sheikh L, Taylor G, Kilby M, Lipkin G: The role of renal biopsy in women with kidney disease identified in pregnancy. *Nephrol Dial Transplant* 23: 201–6, 2008
7. Kida H, Takeda S, Yokoyama H, Tomosugi N, Abe T, Hattori N: Focal glomerular sclerosis in pre-eclampsia. *Clin Nephrol* 24: 221–7, 1985
8. Nochy D, Hinglais N, Jacquot C, Gaudry C, Remy P, Bariety J: De novo focal glomerular sclerosis in preeclampsia. *Clin Nephrol* 25: 116–21, 1986
9. Nagai Y, Arai H, Washizawa Y, Ger Y, Tanaka M, Maeda M, Kawamura S: FSGS-like lesions in pre-eclampsia. *Clin Nephrol* 36: 134–40, 1991
10. Gärtner HV, Sammoun A, Wehrmann M, Grossmann T, Junghans R, Weihing C: Preeclamptic nephropathy – an endothelial lesion. *Eur J Obstet Gynecol Reprod Biol* 77: 11–27, 1998

11. Baylis C: The mechanism of the increase in glomerular filtration rate in the twelve-day pregnant rat. *J Physiol* 305: 405–14, 1980

12. Odutayo A, Hladunewich M: Obstetric nephrology: renal hemodynamic and metabolic physiology in normal pregnancy. *Clin J Am Soc Nephrol* 7: 2073–80, 2012

13. D'Agati VD, Alster JM, Jennette JC, Thomas DB, Pullman J, Savino DA, Cohen AH, Gipson DS, Gassman JJ, Radeva MK, Moxey-Mims MM, Friedman AL, Kaskel FJ, Trachtman H, Alpers CE, Fogo AB, Greene TH, Nast CC: Association of histologic variants in FSGS clinical trial with presenting features and outcomes. *Clin J Am Soc Nephrol* 8: 399–406, 2013

14. Craici IM, Wagner SJ, Bailey KR, Fitz-Gibbon PD, Wood-Wentz CM, Turner ST, Hayman SR, White WM, Brost BC, Rose CH, Grande JP, Garovic VD: Podocyturia predates proteinuria and clinical features of preeclampsia: Longitudinal prospective study. *Hypertension* 61: 1289–1296, 2013

15. White WM, Garrett AT, Craici IM, Wagner SJ, Fitz-Gibbon PD, Butters KA, Brost BC, Rose CH, Grande JP, Garovic VD: Persistent urinary podocyte loss following preeclampsia may reflect subclinical renal injury. *PLoS One* 9: e92693, 2014

16. Garovic VD, Craici IM, Wagner SJ, White WM, Brost BC, Rose CH, Grande JP, Barnidge DR: Mass spectrometry as a novel method for detection of podocyturia in pre-eclampsia. *Nephrol Dial Transplant* 28: 1555–1561, 2013

17. Garovic VD, Wagner SJ, Petrovic LM, Gray CE, Hall P, Sugimoto H, Kalluri R, Grande JP: Glomerular expression of nephrin and synaptopodin, but not podocin, is decreased in kidney sections from women with preeclampsia. *Nephrol Dial Transplant* 22: 1136–43, 2007

18. Zhao S, Gu X, Groome LJ, Wang Y: Decreased nephrin and GLEPP-1, but increased VEGF, Flt-1, and nitrotyrosine, expressions in kidney tissue sections from women with preeclampsia. *Reprod Sci* 16: 970–9, 2009

19. Hara M, Yanagihara T, Kihara I: Urinary podocytes in primary focal segmental glomerulosclerosis. *Nephron* 89: 342–7, 2001

20. Wickman L, Afshinnia F, Wang SQ, Yang Y, Wang F, Chowdhury M, Graham D, Hawkins J, Nishizono R, Tanzer M, Wiggins J, Escobar GA, Rovin B, Song P, Gipson D, Kershaw D, Wiggins RC: Urine podocyte mRNAs, proteinuria, and progression in human glomerular diseases. *J Am Soc Nephrol* 24: 2081–95, 2013
21. Kincaid-Smith P: The renal lesion of preeclampsia revisited. *Am J Kidney Dis* 17: 144–8, 1991
22. Hladunewich MA, Myers BD, Derby GC, Blouch KL, Druzin ML, Deen WM, Naimark DM, Lafayette RA: Course of preeclamptic glomerular injury after delivery. *Am J Physiol Renal Physiol* 294: F614-20, 2008
23. Murakami S, Saitoh M, Kubo T, Koyama T, Kobayashi M: Renal disease in women with severe preeclampsia or gestational proteinuria. *Obstet Gynecol* 96: 945–9, 2000
24. Vikse BE, Irgens LM, Bostad L, Iversen BM: Adverse perinatal outcome and later kidney biopsy in the mother. *J Am Soc Nephrol* 17: 837–45, 2006
25. Vikse BE, Irgens LM, Leivestad T, Skjaerven R, Iversen BM: Preeclampsia and the risk of end-stage renal disease. *N Engl J Med* 359: 800–9, 2008
26. Vikse BE, Hallan S, Bostad L, Leivestad T, Iversen BM: Previous preeclampsia and risk for progression of biopsy-verified kidney disease to end-stage renal disease. *Nephrol Dial Transplant* 25: 3289–96, 2010
27. Smyth A, Oliveira GHM, Lahr BD, Bailey KR, Norby SM, Garovic VD: A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. *Clin J Am Soc Nephrol* 5: 2060–8, 2010
28. Cornelis T, Odutayo A, Keunen J, Hladunewich M: The kidney in normal pregnancy and preeclampsia. *Semin Nephrol* 31: 4–14, 2011
29. Hypertension in pregnancy: diagnosis and management | Guidance and guidelines | NICE. http://www.nice.org.uk/guidance/CG107. Last accessed 28.07.2016.
30. Morris RK, Riley RD, Doug M, Deeks JJ, Kilby MD: Diagnostic accuracy of spot urinary protein and albumin to creatinine ratios for detection of significant proteinuria or adverse pregnancy outcome in patients with suspected pre-eclampsia: systematic

review and meta-analysis. *BMJ* 345: e4342, 2012

31. Pamella S Ochoa JAV: Comparison of 24-Hour Urine to Estimated Renal Function using CKD-EPI, MDRD4 and Cockcroft-Gault in Specific Patient Subsets. *J Pharm Care Heal Syst* 2: 2015

32. Stettler RW, Cunningham FG: Natural history of chronic proteinuria complicating pregnancy. *Am J Obstet Gynecol* 167: 1219–24, 1992

33. Piccoli GB, Daidola G, Attini R, Parisi S, Fassio F, Naretto C, Deagostini MC, Castelluccia N, Ferraresi M, Roccatello D, Todros T: Kidney biopsy in pregnancy: evidence for counselling? A systematic narrative review. *BJOG* 120: 412–27, 2013

404 **Table 1. Demographics of women of childbearing age - all diagnoses**

	Controls	Pregnancy Related (Antenatal & Post-pregnancy)	P Value	Antenatal	Post-pregnancy	P Value
N =	1000	173		19	154	
Median Age Years (IQR)	34.2 (28.0, 41.0)	32.1 (27.8, 36.5)	0.004[a]	30.9 (25.5, 36.0)	32.2 (28.4, 36.9)	0.25[b]
Ethnicity N (%)						
White	324 (32.4)	53 (30.6)	0.65[a]	8 (42.1)	45 (29.2)	0.29[b]
Mixed	12 (1.2)	2 (1.2)	0.96[a]	0 (0.0)	2 (1.3)	>0.99[b]
Asian/Asian British	141 (14.1)	18 (10.4)	0.19[a]	1 (5.3)	17 (11.0)	0.70[b]
Black/Black British	133 (13.3)	45 (26.0)	<0.001[a]	7 (36.8)	38 (24.7)	0.27[b]
Other Groups	97 (9.7)	14 (8.1)	0.50[a]	2 (10.5)	12 (7.8)	0.65[b]
Not stated	293 (29.3)	41 (23.7)	0.13[a]	1 (5.3)	40 (26.0)	0.05[b]
N =	825	152		16	136	
Median SCr at time of biopsy mg/dl (IQR)	1.11 (0.77, 2.06)	0.90 (0.74, 1.51)		0.79 (0.63, 1.33)	0.90 (0.74, 1.58)	0.18[b], 0.002[c]
Median CKD-EPI GFR at time of biopsy ml/min per 1.73m^2 (IQR)	65.9 (30.8, 102.6)	85.7 (47.6, 114.1)		108.2 (60.4, 130.2)	84.1 (46.8 (112.3)	<0.001[c]
N =	609	131		14	117	
Median Urine PCR at time of biopsy mg/mmol (IQR)	240.0 (100.0, 576.0)	237.0 (125.0, 580.0)		536.5 (280.3, 824.5)	200.0 (121.0, 503.5)	0.02[b], 0.80[c]

405 **SCr = Serum Creatinine, PCR = Protein: Creatinine Ratio, IQR = interquartile range, [a]comparison between Controls and Pregnancy-Related**
406 **(Antenatal & Post-pregnancy), [b]comparison between Antenatal and Post-pregnancy, [c]comparison between Controls and Post-pregnancy.**

Table 2. Renal biopsy diagnoses in women of childbearing age comparing disease identified in pregnancy with controls

	Controls	Pregnancy Related (Antenatal & Post-pregnancy)	P Value[a]	Adjusted for Age & Ethnicity (95% CI)[a]		Antenatal	Post-pregnancy	P Value[b]
				OR (95% CI)	P Value			
N =	1000	173				19	154	
FSGS N (%)	97 (9.7)	56 (32.4)	<0.001	4.42 (3.00 to 6.55)	<0.001	6 (31.6)	104 (32.5)	>0.99
Lupus N (%)	235 (23.5)	24 (13.9)	0.005	0.44 (0.28 to 0.70)	0.001	5 (26.3)	19 (12.3)	0.15
IgA N (%)	147 (14.7)	25 (14.5)	0.93	1.10 (0.69 to 1.76)	0.69	1 (5.3)	24 (15.6)	0.32
Interstitial Nephritis N (%)	62 (6.2)	8 (4.6)	0.42	0.74 (0.35 to 1.59)	0.45	0 (0.0)	8 (5.2)	0.60
Membranous N (%)	53 (5.3)	9 (5.2)	0.96	1.01 (0.48 to 2.10)	0.99	2 (10.5)	7 (4.5)	0.26
Minimal Change N (%)	50 (5.0)	5 (2.9)	0.23	0.59 (0.23 to 1.51)	0.27	0 (0.0)	5 (3.2)	>0.99
Thin Membrane N (%)	30 (3.0)	9 (5.2)	0.14	2.11 (0.97 to 4.60)	0.06	0 (0.0)	9 (5.8)	0.60
DM N (%)	35 (3.5)	1 (0.6)	0.04	0.18 (0.25 to 1.42)	0.10	0 (0.0)	1 (0.7)	>0.99
Crescentic N (%)	14 (1.4)	0 (0.0)	0.12	1.0 (-)	-	0 (0.0)	0 (0.0)	>0.99
FSGS (HIV) N (%)	6 (0.6)	1 (0.6)	0.97	0.51 (0.06 to 4.37)	0.54	0 (0.0)	1 (0.6)	>0.99
Other N (%)	271 (27.1)	35 (20.2)	0.06	0.73 (0.50 to 1.08)	0.12	5 (26.3)	30 (19.5)	0.54

OR = Odds Ratio, CI = Confidence Interval, [a]comparison between Controls and Pregnancy-Related (Antenatal & Post-pregnancy), [b]comparison between Antenatal and Post-pregnancy, - logistic regression failed.

412 **Table 3. Demographics of women of childbearing age with FSGS**

	Controls	Pregnancy Related (Antenatal & Post-pregnancy)	P Value	Antenatal	Post-pregnancy	P Value
N =	97	56		6	50	
Median Age Years (IQR)	35.7 (30.3, 41.9)	33.4 (27.3, 39.1)	0.05[a]	29.5 (22.5, 37.1)	33.7 (28.7, 39.2)	0.26[b]
Ethnicity N (%)						
White	29 (29.9)	18 (32.1)	0.77[a]	3 (50.0)	15 (30.0)	0.38[b]
Mixed	1 (1.0)	1 (1.8)	0.69[a]	0 (0.0)	1 (2.0)	>0.99[b]
Asian/AsianBritish	10 (10.3)	4 (7.1)	0.51[a]	0 (0.0)	4 (8.0)	>0.99[b]
Black/Black British	22 (22.7)	18 (32.1)	0.20[a]	3 (50.0)	15 (30.0)	0.37[b]
Other Groups	9 (9.3)	2 (3.8)	0.19[a]	0 (0.0)	2 (4.0)	>0.99[b]
Not stated	26 (26.8)	13 (23.2)	0.62[a]	0 (0.0)	13 (26.0)	0.32[b]
Columbia Classification N (%)						
Cellular	3 (3.1)	3 (5.4)	0.49[a]	1 (16.7)	2 (4.0)	0.29[b]
Collapsing	7 (7.2)	1 (1.8)	0.15[a]	0 (0.0)	1 (2.0)	>0.99[b]
NOS	67 (69.1)	38 (67.9)	0.88[a]	5 (83.3)	33 (66.0)	0.65[b]
Perihilar	8 (8.2)	8 (14.3)	0.24[a]	0 (0.0)	8 (16.0)	0.58[b]
Tip	8 (8.2)	6 (10.7)	0.61[a]	0 (0.0)	6 (12.0)	>0.99[b]
Not Classified	4 (4.1)	0 (0.0)	0.12[a]	0 (0.0)	0 (0.0)	>0.99[b]
N =	79	49		5	44	
Median SCr at time of biopsy mg/dl (IQR)	1.07 (0.84, 1.75)	0.92 (0.72,1.32)		0.92 (0.64, 1.48)	0.93 (0.75, 1.29)	0.85[b],0.04[c]
Median CKD-EPI GFR at time of biopsy ml/min per 1.73m^2 (IQR)	71.6 (41.2, 92.6)	86.0 (58.3, 112.0)		102.1 (49.5, 135.7)	85.4 (58.4, 110.2)	0.02[c]
N =	72	43		5	38	
Median Urine PCR at time of biopsy mg/mmol (IQR)	340.0 (165.0, 629.5)	237.0 (160.0, 600.0)		600.0 (250.0, 708.0)	200.0 (157.5, 495.3)	0.17[b], 0.27[c]

413 **SCr = Serum Creatinine, PCR = Protein: Creatinine Ratio, IQR = interquartile range, [a]comparison between Controls and Pregnancy-Related**
414 **(Antenatal & Post-pregnancy), [b]comparison between Antenatal and Post-pregnancy, [c]comparison between Controls and Post-pregnancy.**

Table 4. Follow-up of women of childbearing age - all diagnoses

	Controls	Pregnancy Related (Antenatal & Post-pregnancy)	P Value	Antenatal	Post-pregnancy	P Value
N =	459	101		14	87	
Median Follow-up Time Months (IQR)	44.3 (20.1, 77.2)	42.8 (17.4, 70.9)	0.48[a]	40.8 (24.2, 75.6)	43.3 (17.0, 70.8)	>0.99[b]
Median Rate of Change in CKD-EPI GFR ml/min per 1.73m^2 per year (IQR)	-0.56 (-4.26, 3.22)	-2.43 (-8.16, 0.18)		-7.36 (-15.44, -4.35)	-1.33 (-6.97, 0.94)	0.002[b], 0.045[c]
Died % (N)	3.4 (34/1000)	2.3 (4/173)	0.46[a]	(10.5) 2/19	1.3 (2/154)	0.06[b]
RRT % (N)	13.0 (130/1000)	12.7 (22/173)	0.92[a]	15.8 (3/19)	12.3 (19/154)	0.72[b]
Time to reach RRT Months (IQR)	18.55 (5.37, 45.79)	17.8 (7.3, 46.5)	0.93[a]	17.8 (11.3, 89.5)	19.8 (4.5, 44.7)	0.53[b]
Age at RRT Years (IQR)	37.9 (30.4, 44.1)	34.0 (27.7, 40.8)	0.27[a]	34.2 (24.9, 40.3)	33.2 (27.7, 42.2)	0.74[b]

RRT = Renal Replacement Therapy, CKD = Chronic Kidney Disease, IQR = interquartile range, [a]comparison between Controls and Pregnancy-Related (Antenatal & Post-pregnancy), [b]comparison between Antenatal and Post-pregnancy, [c]comparison between Controls and Post-pregnancy.

Table 5. Follow-up in women of childbearing age with FSGS

	Controls	Pregnancy Related (Antenatal & Post-pregnancy)	P Value	Antenatal	Post-pregnancy	P Value
N =	49	31		4	27	
Median Follow-up Time Months (IQR)	45.9 (26.3, 92.6)	48.0 (30.6, 75.9)	0.83[a]	41.9 (37.0, 78.3)	50.3 (20.0, 75.9)	>0.99[b]
Median Rate of Change in CKD-EPI GFR ml/min per 1.73m^2 per year (IQR)	-1.98 (-5.98, 0.26)	-2.66 (-8.97, 0.00)		-8.48 (-12.85, -6.89)	-1.62 (-7.55, 0.21)	0.06[b], 0.91[c]
Died %	3.1 (3/97)	1.8 (1/56)	0.63[a]	16.7 (1/6)	0.0 (0/50)	0.11[b]
RRT %	15.5 (15/97)	7.1 (4/56)	0.13[a]	16.7 (1/6)	6.0 (3/50)	0.37[b]
Time to reach RRT Months (IQR)	46.0 (12.99, 68.13)	64.7 (50.3, 89.5)	0.17[a]	89.5	57.5 (50.3, 64.7)	-
Age at RRT Years (IQR)	39.3 (33.4,46.6)	40.3 (32.1, 40.3)	0.77[a]	40.3	36.2 (32.1, 40.3)	-

RRT = Renal Replacement Therapy, CKD = Chronic Kidney Disease, IQR = interquartile range, [a]comparison between Controls and Pregnancy-Related (Antenatal & Post-pregnancy), [b]comparison between Antenatal and Post-pregnancy, [c]comparison between Controls and Post-pregnancy.

427 **Figure 1. Identification and assembly of matched cohorts**